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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF IVERMECTIN LOADED EMULGEL

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ABSTRACT

Emulgel is the topical drug dosage form in which emulsions are gelled by mixing with gelling agents. Incorporation of emulsion into gel increases the stability of emulsion and provides the controlled release system. Emulgel is the promising drug delivery system for delivering of hydrophobic drugs. Emulgel has several favorable properties for dematological use such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf life, and pleasant appearance. They have the dual drug releasing system *i.e.,* gel and emulsion. The purpose of the present study was to develop and optimize the emulgel system for Ivermectin using Carbopol 941 gelling agent. The prepared emulgels were evaluated in terms of appearance, pH, spreadability, viscosity, drug content and *in-vitro* drug release. *In-vitro* diffusion studies were carried out using pH 7.4 phosphate buffer and formulation F3 (Carbopol 941-1%) has shown best results with zero order release kinetics and diffusion mechanism.

Keywords: Ivermectin, Topical drug delivery system, Carbopol 941, Emulgel, Diffusion mechanism.

1. INTRODUCTION

Rosacea is a common chronic relapsing inflammatory skin condition which mostly affects the central face, with women being more affected than men [1]. The pathophysiology is not completely understood, but dysregulation of the immune system, as well as changes in the nervous and the vascular system have been identified. Microbes that are part of the normal skin flora, and specifically in the pilo-sebaceous unit-including *Demodex* mites and *Staphylococcus epidermidis* may also play a role as triggers of rosacea [2-3]. Symptoms are initially transient followed by persistent erythema due to repeated vasodilation, then telangiectasia and skin inflammation in the form of papules, pustules, lymphoedema and fibrosis [4]. Emulgels are emulsions, either of the oil-in-water or water in oil type which are gelled by mixing with gelling agent. Emulsified gel is stable one and superior vehicle for hydrophobic or poorly water soluble drugs. In short, emulgels are the combination of emulsion and gel [5]. Emulsions possess a certain degree of elegance and are easily washed off whenever desired. They also have a high ability to penetrate the skin. Emulgels for dermatological use have several favourable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining and transparent with long shelf life and pleasing appearance [6]. The aim of this work was to develop and optimize emulgel formulation of Ivermectin for effective topical treatment. Ivermectin is a broad-spectrum anti-parasite medication. Ivermectin is mainly used in humans in the treatment of onchocerciasis, but is also effective against other worm infestations (such as strongyloidiasis, ascariasis, trichuriasis and enterobiasis). Topical ivermectin appeared to be more effective for papulopustular rosacea.

2. MATERIAL AND METHODS

2.1. Material

Carbomer 941, Liquid paraffin, Span 20, Tween 20, Propylene glycol were procured from S.D. Fine Chem. Ltd, and Loba Chemie, Mumbai (India). All other chemicals and reagents used were of analytical grade. Deionised distilled water was used throughout the study.

2.2. Formulation development

The general method employed for preparation of an emulsion was as follows: The oil phase was prepared by dissolving Span 20 in liquid paraffin in the different ration given as in table 1, while the aqueous phase was prepared by dissolving Tween 20 in purified water [7]. One gram of Ivermectin was dissolved in 5 ml of ethanol, while 0.15 g of methylparaben and 0.05 g of propylparaben were dissolved in 5 gm of propylene glycol and both were mixed with aqueous phase. Both the oily and

aqueous phases were separately heated to 70-80°C. Then, the oil phase was added to the aqueous phase with continuous stirring at 500 rpm until cooled to room temperature.

2.3. Preparation of carbopol gel

Fifty (50) grams of the carbopol gel was prepared by dispersing 1 gram of carbopol powder in 50 ml purified water with aid of moderate speed stirrer (50 rpm), and then the pH was adjusted to 6.5-6.8 using 0.5 N of sodium hydroxide [8].

2.4. Formulation of Ivermectin emulgel

Six formulations of Ivermectin were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until get homogenous emulgel formulations is shown in table 1.

Table 1: Different formulations of ivermectin emulgel (% w/w)

Formulation	Ivermectin (mg)	Carbomer 941	Liquid paraffin	Span 20	Tween 20	Propylene glycol	water
F1	500	0.5	5	2	5	5	100
F2	500	0.5	5	2	10	5	100
F3	500	1.0	10	4	5	5	100
F4	500	1.0	10	4	10	5	100
F5	500	1.5	5	2	5	5	100
F6	500	1.5	5	2	10	5	100

2.5. Characterization of emulgel

2.5.1. Physical appearance

The formulated emulgels were examined for their colour, clogging, homogeneity and texture after 24hr of preparation [9].

2.5.2. Determination of pH

The pH values of 1% aqueous solutions of the prepared emulgels were measured by a calibrated pH meter [10]. The results are represented in table 2.

2.5.3. Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually and observations were noted [11].

2.5.4. Extrudability study

The emulgel formulations were filled into collapsible metal tubes or aluminium collapsible tubes [12]. The tubes were pressed to extrude the material and the extrudability of the formulation was checked.

2.5.5. Spreadability

Two glass slides of standard dimensions (6×2) were selected. The emulgel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the emulgel formulation between the two slides was traced uniformly to form a thin layer. The weight was removed and the excess of the emulgel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied 50 with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each emulgel formulation [13].

Spreadability = m.l/t

Where, S=Spreadability (gcm/sec), m = weight tied to the upper slide (20 grams), l= length of glass slide (6 cms), t = time taken is seconds.

2.5.6. Viscosity

The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer [14]. The viscosity was measured using spindle no. 6 at 10 rpm and 25°C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature (25±/1°C) before the measurements.

2.5.7. Drug content

1 gm. of the prepared gel was mixed with 100 ml. of ethanol. Aliquots of different concentrations were

prepared by suitable dilutions after filtering the stock solution and the absorbance was measured at 246 nm. Drug content was calculated by linear regression analysis of the calibration curve.

2.6. *In-vitro* drug release studies using the prehydrated cellophane membrane

The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15 mm internal diameter and 100mm height. The diffusion cell membrane was applied with 1 gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing 7.4 pH phosphate buffer, freshly prepared as a receptor base and the system was maintained for 2 hrs at 37±0.5°C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of upto 12 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 246 nm using neutralizing 7.4 pH phosphate buffer as blank [15].

3. RESULTS AND DISCUSSION

The present work was aimed to increase the penetration through skin by formulating emulgels with Carbopol 941 gelling agent. The prepared formulations were characterized for physical appearance, pH, spreadability, viscosity, drug content, *in- vitro* drug release.

Table 2: Physical appearance

Formulation	Washability	Extrudability	Observation	Clogging	Homogeneity
F1	+++	++	white cream	Absent	Good
F2	+++	++	white cream	Absent	Good
F3	+++	+++	white cream	Absent	Good
F4	+++	+++	white cream	Absent	Good
F5	+++	+	white cream	Present	Average
F6	+++	+	white cream	Present	Average

Excellent: +++, Good: ++, Average: +, Poor: -

Table 3: Results of Viscosity, pH, % Drug content and Spreadability

Formulation	Viscosity (cps)	pH	% Drug content	Spreadability (gcm/sec)
F1	3265	6.92	97.56	13.56
F2	3345	6.73	98.85	12.78
F3	4214	6.84	99.12	11.45
F4	4315	6.68	98.74	14.65
F5	4522	6.77	98.65	13.25
F6	4598	6.91	98.12	12.78

Table 4: *In vitro* drug release data for optimized formulation F3

S. No.	Time (min)	Square Root of Time	Log Time	Cumulative* Percentage Drug Release ± SD	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log cumulative Percent Drug Remaining
1	15	3.873	0.588	26.65	1.426	73.35	1.865
2	30	5.477	0.739	39.98	1.602	60.02	1.778
3	45	6.708	0.827	48.84	1.689	51.16	1.709
4	60	7.746	0.889	62.12	1.793	37.88	1.578
5	120	10.954	1.04	78.85	1.897	21.15	1.325
6	240	15.492	1.19	98.84	1.995	1.16	0.064

** Average of three determinations*

Table 5: Regression analysis data of optimized formulation F3

Batch	Zero Order	First Order
	R^2	
F3	0.890	0.753

All the prepared formulations were found to be white, clogging was found to be absent and having good homogeneity. Spreadability of formulation F1, F2, F3, F4, F5 and F6 was found to be 13.56, 12.78, 11.45, 14.65, 13.25 and 12.78gcm/sec respectively. The pH of all formulation was found to be near to skin pH. The pH of formulation F1, F2, F3, F4, F5 and F6 was found to be 6.92, 6.73, 6.84, 6.68, 6.77 and 6.91 respectively.

The Viscosity of formulation F1, F2, F3, F4, F5 and F6 was found to be 3265, 3345, 4214, 4315, 4522 and 4598cps respectively. The drug content of prepared emulgel formulation was found to be near to 100%. The drug content of formulation F1, F2, F3, F4, F5 and F6 was found to be 97.56, 98.85, 99.12, 98.74, 98.65 and 98.12 percent.

The drug release of drug through prehydrated cellophane membrane was found to be 71.14, 69.98, 98.84, 86.65, 79.98 and 75.56 for formulation F1, F2, F3, F4, F5 and F6 after 6hrs. It can be concluded from the above results and discussion that Ivermectin emulgel formulations prepared with Carbomer 941, Liquid paraffin, Span 20, Tween 20 and Propylene glycol showed acceptable physical properties, drug content and drug release. The optimized batch F3 of emulgel showed good drug release of 98.84% after 4 hrs.

4. CONCLUSION

In vitro drug release from the semisolid preparation of Ivermectin emulgel optimized formulation F3 shows significantly improved in drug release rate as compared to marketed preparation. Hence it could be concluded that the carbomer based semisolid preparation would be providing local onset of action without need of any device for their application on skin. The preparation of emulgel has potential advantages over marketed preparation as they improved patient compliance rapid local onset of action for longer period with cost effectiveness. The pediatric and geriatric populations are the primary ones whose problems are easily targeted.

Conflict of interest

None declared

5. REFERENCES

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